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Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Lowering With Atorvastatin in Patients of South Asian Compared With European Origin: Insights From the Achieve Cholesterol Targets Fast With Atorvastatin Stratified Titration (ACTFAST) Study

Milan Gupta, MD, Pierre Martineau, MSc, PharmD, BCPS, Thang Tran, MSc, Jean-Pierre Després, PhD, FAHA, Allan Gaw, MD, PhD, MRCPath, MFPM, Eduardo de Teresa, MD, FESC, Csaba Farsang, MD, DSc, Gian Franco Gensini, MD, Lawrence A. Leiter, MD, FRCPC, FACP, Luis Miguel Blanco-Colio, PhD, Jesús Egido, MD, PhD, and Anatoly Langer, MD, on behalf of the ACTFAST investigators

The aim of this study was to determine the effects of atorvastatin in patients of South Asian versus European origin who participated in the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. ACTFAST was a 12-week prospective, open-label study in patients at high risk for atherosclerosis (European origin, n = 1978; South Asian origin, n = 64). Compared with patients of European origin, patients of South Asian origin were younger, were less likely to smoke, and had lower body mass index, systolic blood pressure, low-density lipoprotein cholesterol (LDL-C) and triglycerides. Because significant differences were observed in baseline characteristics between patient groups, case control propensity scores were used. In the unmatched analysis, South Asians had greater LDL-C response to atorvastatin than patients of European origin. However, after propensity matching, atorvastatin lowered LDL-C and high-sensitivity C-reactive protein (hs-CRP) to a similar degree in both groups, with no differences in safety profile. The authors observed no correlation between change in hs-CRP and LDL-C concentrations in either population. In conclusion, atorvastatin lowered both LDL-C and hs-CRP to a similar degree in patients of South Asian or European origin, suggesting usual starting doses of atorvastatin (with appropriate monitoring), rather than lower starting doses as has been advocated by some, may be used in patients of South Asian origin.

Keywords: *South Asians; ethnicity; coronary artery disease; statins; low-density lipoprotein cholesterol*

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It is recognized that South Asians (defined as individuals with ancestral origins in the Indian subcontinent: India, Pakistan, Bangladesh, Nepal, and Sri Lanka) are at increased risk of coronary heart disease (CHD).[1,2] Current data show that people of South Asian origin are 40% to 50% more likely to die from heart disease when compared with those of European origin.[2,3] South Asians are generally

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younger at the time of first myocardial infarction or development of heart failure, have larger myocardial infarctions, and have more severe coronary disease on angiography.[4-6]

An excess of conventional cardiovascular risk factors does not fully account for the excess risk of CHD observed in South Asians.[4] Although diabetes has been shown to be more common in South Asians, other conventional risk factors such as smoking, hyperlipidemia, increased body mass index (BMI), hypertension, and previous vascular disease have generally been found to occur with similar or lower frequency among South Asians compared with control participants.[1,4] Thus, it has been proposed that novel risk factors may play a dominant role in the development of atherosclerosis in South Asians. Lipoprotein(a), apolipoprotein B (apo-B), homocysteine, plasminogen activator inhibitor–1, fibrinogen, and C-reactive protein (CRP) have generated considerable interest. Blood concentrations of lipoprotein(a), homocysteine, and plasminogen activator inhibitor–1 tend to be higher in patients of South Asian compared with those of European origin.[1] However, in current practice, South Asians are typically not screened for these emerging risk factors. Clinical trials have not enrolled sufficient numbers of South Asians to guide clinical practice, and consequently, diagnosis and treatment recommendations are derived primarily from studies performed in people of European origin.

Although dyslipidemia may not occur at a higher rate among South Asians, the type of dyslipidemia does seem to differ.[1] People of South Asian origin have been found to have higher total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein(a) and lower high-density lipoprotein (HDL-C) levels compared with populations of Chinese or European origin.[1]

Statin safety and efficacy data are mainly derived from populations of North American or European origin, which may not translate to similar results in patients of South Asian origin. For example, South Asians administered rosuvastatin have twice the drug concentration compared with patients of European origin treated with an equivalent dose,[7,8] leading to a recommendation that South Asians should be started on a lower dose of rosuvastatin or at least be more carefully monitored.

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) trial investigated whether selecting the starting dose of atorvastatin according to baseline and target LDL-C values would allow high-risk subjects to achieve target LDL-C concentrations rapidly, with either no titration or just 1 titration step, regardless of statin use at baseline. Atorvastatin reduces LDL-C levels by up to 60% and is well tolerated up to its maximum dose of 80 mg.[9] In addition, it has been shown to slow the progression of atherosclerosis[10] and reduce the incidence of cardiovascular events in both primary and secondary prevention of CHD.[11-13]

People of South Asian origin represent a large and growing population, and their underrepresentation in clinical trials is of concern. This article presents the results of a prespecified substudy of the ACTFAST trial performed to determine whether LDL-C and high-sensitivity CRP (hs-CRP) response to atorvastatin is altered in high-risk patients of South Asian compared with those of European origin.

METHODS

Patient Population

The study design of ACTFAST has been described in detail elsewhere[14] and is summarized below (Figure 1). ACTFAST was a 12-week, multicenter, prospective, open-label trial assessing the effectiveness of using starting doses of atorvastatin selected based on baseline LDL-C and on the required LDL-C reduction to reach the target. High-risk patients aged 18 years and older were eligible for inclusion if they had dyslipidemia, defined as LDL-C >2.6 mmol/L (100 mg/dL) and ≤5.7 mmol/L (220 mg/dL) at screening, triglycerides ≤6.8 mmol/L (600 mg/dL), and a history of

From Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Dr Gupta); St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Dr Gupta, Dr Leiter, Dr Langer); Canadian Cardiovascular Research Network, Brampton, Ontario, Canada (Dr Gupta); Medical Division, Pfizer Canada, Kirkland, Québec, Canada (Dr Martineau, Mr Tran); Quebec Heart & Lung Institute, Université Laval, Québec, Canada (Dr Després); University of Glasgow, Glasgow, UK (Dr Gaw); University of Malaga, V. de la Victoria Hospital, Malaga, Spain (Dr de Teresa); Cardiometabolic Department, St Imre Teaching Hospital, Budapest, Hungary (Dr Farsang); Department of Medical and Surgical Critical Care, University of Florence, Department of Heart and Vessels, Azienda Ospedaliero-Universitaria Careggi Hospital, Firenze, Italy (Dr Gensini); Vascular Research Laboratory, Fundación Jimenéz Díaz, Autonoma University, Madrid, Spain (Dr Blanco-Colio, Dr Egido); and Canadian Heart Research Centre, Toronto, Ontario, Canada (Dr Langer), on behalf of the ACTFAST investigators. Submitted for publication January 17, 2011; revised version accepted March 18, 2011. Address for correspondence: Milan Gupta, MD, William Osler Health Centre, 200-3 Conestoga Drive, Brampton, ON, L6Z 4N5, Canada; e-mail: mkgupta@rogers.com.

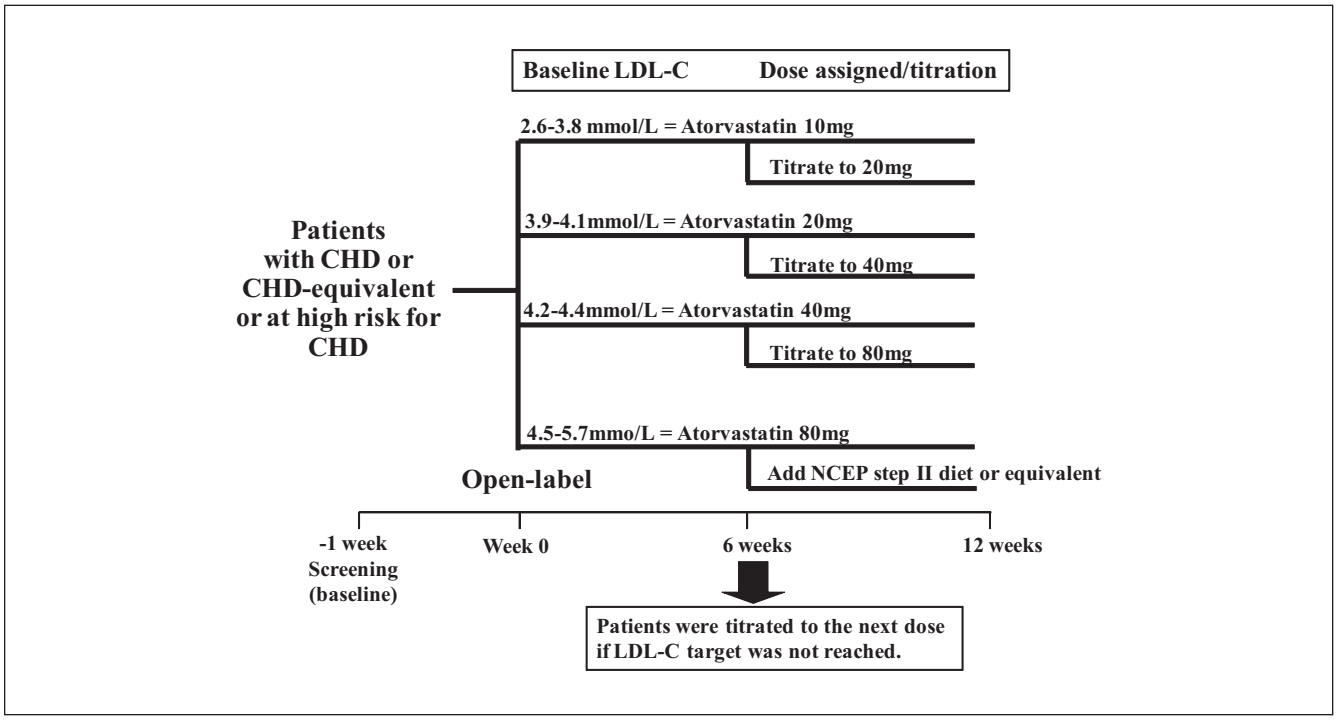

Figure 1. Study design. To convert mmol/L to mg/dL, multiply by 38.65. CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; NCEP: National Cholesterol Education Program. Adapted from Martineau et al.[14]

CHD, a CHD equivalent (diabetes, cerebrovascular disease, or peripheral vascular disease), or an estimated 10-year CHD risk >20% as per the Framingham tables.[15] Patients could be either statin free or statin treated at baseline and had to be willing to follow the National Cholesterol Education Program (NCEP) III multifaceted lifestyle approach (or local equivalent).[15] Patient ethnicity was self-reported.

Patients were considered ineligible for the study if they were receiving therapy with any statin at a dose >40 mg/d*, atorvastatin, fibrates, niacin or resins that could not be discontinued a minimum of 2 months prior to enrollment, or strong inhibitors of CYP3A4. Patients were also excluded if they suffered from specific systemic diseases, including impaired hepatic (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥2 times the upper limit of normal) or renal function (creatinine ≥181 µmol/L), uncontrolled diabetes (A1c >10%), uncontrolled hypertension (>160/100 mm Hg), uncontrolled primary hypothyroidism (thyroid stimulating hormone ≥1.5 times the upper limit of normal), evidence of gastrointestinal disease limiting drug absorption or partial ileal bypass, elevation of creatine kinase (CK) level (>3 times the upper limit of normal), alcohol and/or any other drug abuse, history of intolerance or hypersensitivity to statins, any severe disease or surgical procedure within 3 months prior to screening, or were women of childbearing potential not using appropriate contraception.

Treatment

Patients were assigned to 6 weeks of open-label treatment with atorvastatin according to their baseline LDL-C level and prior statin use, followed by an additional 6-week open-label treatment during which patients who had not reached target LDL-C levels were titrated to the next highest dose of atorvastatin. Patients who were statin free with a baseline LDL-C of 100 to 149 mg/dL (2.6-3.8 mmol/L), 150 to 159 (3.9-4.1 mmol/L), 160 to 169 (4.2-4.4 mmol/L), and 170 to 220 mg/dL (4.5-5.7 mmol/L) were assigned to 10, 20, 40 and 80 mg of atorvastatin, respectively. Patients on a statin at baseline but

*Rosuvastatin became commercially available in Canada and the United Kingdom during the trial, and the Steering Committee allowed patients on 10 mg to be enrolled in the study.

whose LDL-C remained above target values received double the atorvastatin dose for the same baseline LDL-C level as compared with their untreated counterparts, without any washout period. Patients with LDL-C 4.5 to 5.7 mmol/L (170–220 mg/dL) all received the 80-mg dose, regardless of statin use at baseline. Patients initially allocated to atorvastatin 80 mg who did not reach LDL-C targets remained on that dose, and a more intense therapeutic lifestyle intervention was recommended.

Blood samples were obtained at screening, week 6, and week 12 for the measurement of 12-hour fasting serum lipid profiles and routine safety blood measurements. Patients received dietary counseling at all visits. The relevant institutional review boards approved the protocol, and informed consent was obtained from all patients. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki.[16]

Efficacy Parameters

The primary efficacy outcome of the main study was the proportion of patients achieving NCEP III target LDL-C levels of <2.6 mmol/L (<100 mg/dL) after 12 weeks of treatment (termed LDL-C responders), using the last observation carried forward technique.[14] The objective of the current substudy was to compare the degree of LDL-C and hs-CRP lowering between patients of South Asian and European origin.

Lipid Assays

Direct measurement of LDL-C was performed using a homogeneous enzymatic colorimetric assay (LDL-C Plus 2nd generation; Roche Diagnostics GmbH, Mannheim, Germany) by a central laboratory accredited for lipid assays by the Centers for Disease Control and Prevention (CDC)/National Heart, Lung, and Blood Institute (NHLBI). This assay is reliable with triglyceride plasma values up to 1200 mg/dL (13.5 mmol/L). Serum hs-CRP was assessed using a high-sensitivity, latex microparticle-enhanced immunoturbidimetric assay (Tina-Quant; Roche Diagnostics GmbH).

Statistical Analysis

Because of significant imbalances in baseline characteristics between patients of South Asian and European origin, a 1:1 ethnicity match on propensity scores was used to reduce imbalance. A multivariate logistic regression model was used to estimate propensity scores of being of South Asian origin. Covariates included in the logistic regression model were age, gender, baseline LDL-C, triglyceride and apo-B concentrations, baseline hs-CRP concentration, diastolic blood pressure (BP), systolic BP, smoking status, diabetes, and history of CHD. Body mass index (BMI) was not included as a covariate because we wanted to compare South Asians and Europeans who had a comparable cardiometabolic risk profile. In addition, it is well known that for a given BMI/waist circumference, South Asians have a greater percentage of body fat and a different pattern of body fat distribution than Europeans.[17] Therefore, the BMI would not be the appropriate anthropometric variable to correct for differences in body fat/fat distribution between the 2 ethnic groups. We then matched each patient of South Asian origin to one of European origin with very similar propensity scores using Greedy matching techniques[18] where the South Asian participants are ordered and sequentially matched to the nearest unmatched European origin. If more than 1 unmatched is found, the matched European origin is selected at random. Statistical analysis was performed using SAS software (SAS, Release 8.2; SAS Institute, Cary, North Carolina). P values <.05 were considered statistically significant. Categorical variables were analyzed using chi-square or Fisher exact test, where appropriate. Continuous variables were examined by t test for baseline characteristics and analysis of covariance (ANCOVA) adjusted for baseline values for change from baseline to week 12. Because of the skewed distribution of serum hs-CRP levels, log-transformed values were used in the analyses and back transformed for data presentation, yielding geometric means. Because of the large difference in group size and because unmatched groups may differ in various aspects, we only performed general safety comparisons.

RESULTS

Study Population

The baseline demographics of patients enrolled in ACTFAST have been described previously.[14] Briefly, the study recruited 2187 patients, including 64 of South Asian and 1978 of European origin. Participants were predominantly men of European origin with a mean age of 64 years. Every South Asian case could be matched with a case of European origin, except for 1 South Asian patient with an extremely high propensity score, thus yielding a total 63 patients in each group.

Table I Baseline Characteristics of the Unmatched Population

Baseline Characteristics	South Asian Origin (n = 64)	European Origin (n = 1978)	*P* Value
Age, y, mean ± SD	59 ± 12	64 ± 11	<.0001
Male, No. (%)	49 (77.0)	1330 (67.2)	.12
BMI, kg/m^2, mean ± SD	26.4 ± 3.6	29.2 ± 5.1	<.0001
LDL-C, mmol/L, mean ± SD	3.6 ± 0.5	3.8 ± 0.7	.003
Apo-B, g/L, mean ± SD	1.1 ± 0.2	1.1 ± 0.2	.12
Triglycerides, mmol/L, mean ± SD	2.2 ± 1.1	1.9 ± 0.9	.038
hs-CRP, mg/L			
Mean (raw data)	4.0 ± 4.5	5.2 ± 9.5	.28
Geometric mean ± SD	2.5 ± 2.7	2.9 ± 2.8	
Smoking status, No. (%)			
Never smoked	43 (67.0)	597 (30.2)	<.0001
Smoker	4 (6.0)	438 (22.1)	
Ex-smoker	17 (27.0)	943 (47.7)	
Blood pressure, mm Hg, mean ± SD			
Systolic	130 ± 16	136 ± 17	<.007
Diastolic	78 ± 11	79 ± 10	.48
Diabetes, No. (%)	32 (50.0)	752 (38.0)	.052
History of CHD, No. (%)	46 (72.0)	1212 (61.3)	.086

Apo-B, apolipoprotein B; BMI, body mass index; CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Baseline Characteristics

The distributions of baseline covariates between patients of South Asian and European origin are displayed in Table I. Significant differences were observed in age, BMI, LDL-C, smoking status, systolic BP, and triglycerides. No differences were observed between the 2 groups for gender, hs-CRP, diastolic BP, history of CHD or diabetes, or apo-B concentrations.

After matching, no statistical differences were found for all observed covariates used in the logistic regression model, suggesting improvement in covariate balance between patients of South Asian and European origin, leading to comparable groups with regard to key baseline metabolic parameters and demographics (Table II).

LDL-C Response

In the unmatched population, the percentage reduction in LDL-C from baseline was significantly greater in patients of South Asian compared with European origin (P = .01; Figure 2). However, in the matched population, no significant difference was observed between the groups (P = .22). The proportion of LDL-C responders (LDL-C <2.6 mmol/L [<100 mg/dL]) after 12 weeks of treatment trended in favor of a higher response rate in patients of South Asian origin (P = .05), but the difference remained nonsignificant in the matched populations (Figure 3).

Hs-CRP Response

The percentage change in hs-CRP was not significantly different between patients of South Asian and European origin, in either the unmatched or matched groups (Figure 4).

Correlation Between LDL-C and Log (hs-CRP) Response

There were no correlations between baseline values of LDL-C and hs-CRP or change from baseline after 12 weeks of treatment in the unmatched or matched populations (Table III). The only exception was a statistically significant, but clinically irrelevant, correlation between change in LDL-C and hs-CRP (r^2 = 0.0024, P = .03) among patients of European origin, only observed in the unmatched population.

Safety

There was no difference in treatment-related or all-causality adverse events in patients of South Asian

Table II Baseline Characteristics of the Matched Case Control Population

Baseline Characteristics	South Asian Origin Cases (n = 63)	Matched European Origin Cases (n = 63)	*P* Value
Age, y, mean ± SD	59 ± 12	59 ± 11	.7
Male, No. (%)	48 (76.0)	49 (77.8)	.83
BMI, kg/m^2, mean ± SD	26.5 ± 3.6	29.5 ± 5.3	.0003
LDL-C, mmol/L, mean ± SD	3.6 ± 0.5	3.5 ± 0.5	.43
Apo-B, g/L, mean ± SD	1.1 ± 0.2	1.1 ± 0.2	.94
Triglycerides, mmol/L, mean ± SD	2.2 ± 1.1	2.3 ± 1.3	.4
hs-CRP, mg/L			
Mean (raw data)	4.0 ± 4.6	3.9 ± 5.1	.32
Geometric mean ± SD	2.5 ± 2.7	2.1 ± 3.1	
Smoking status, No. (%)			
Never smoked	43 (68.0)	41 (65.1)	.8
Smoker	4 (6.0)	3 (4.8)	
Ex-smoker	16 (25.0)	19 (30.2)	
Blood pressure, mm Hg, mean ± SD			
Systolic	130 ± 16	131 ± 17	.75
Diastolic	78 ± 11	79 ± 9	.78
Diabetes, No. (%)	32 (51.0)	32 (50.8)	1.0
History of CHD, No. (%)	45 (71.0)	45 (71.4)	1.0

Apo-B, apolipoprotein B; BMI, body mass index; CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

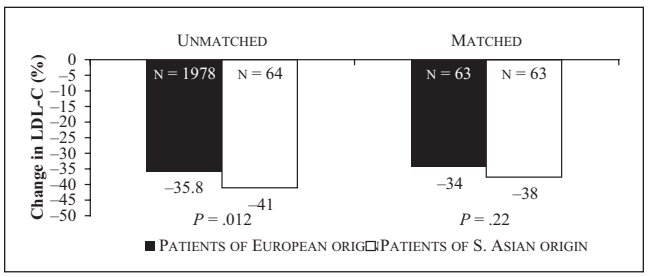

Figure 2. Percentage change in LDL-C from baseline to week 12 (last observation carried forward). LDL-C, low density lipoprotein-cholesterol.

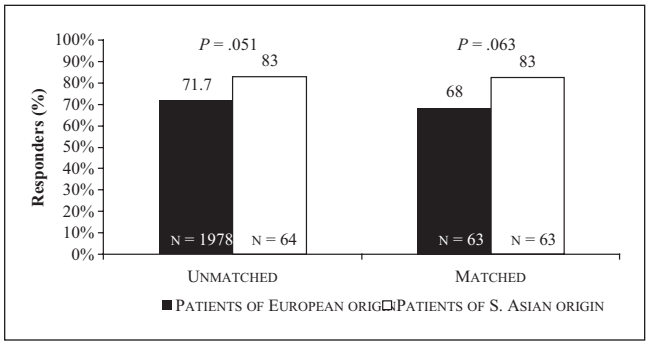

Figure 3. Proportion of LDL-C responders at week 12 (last observation carried forward). LDL-C, low density lipoprotein-cholesterol. Response is defined by an LDL-C below 2.6 mmol/L (<100 mg/dL).

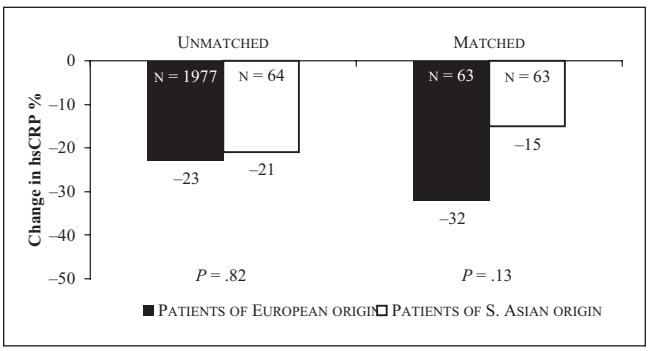

Figure 4. Percentage change in hs-CRP from baseline to week 12 (last observation carried forward). hs-CRP, high-sensitivity C-reactive protein.

or European origin. Overall, the incidence of adverse events in South Asians was either lower than or similar to patients of European origin (Table IV).

DISCUSSION

Compared with patients of European origin, those of South Asian origin enrolled in ACTFAST were younger and leaner, smoked less, and exhibited lower systolic BP and LDL-C but had higher triglyceride levels, despite lower BMI values. This difference

Table III Correlation Between LDL-C and Log (hs-CRP) (LOCF)

	Unmatched Population	Matched Case Control Population
Baseline	EO: $r^2 = 0.00052$; $P = .31$	EO: $r^2 = 0.010$; $P = .43$
	SAO: $r^2 = 0.0075$; $P = .50$	SAO: $r^2 = 0.0055$; $P = .56$
Change from baseline to week 12	EO: $r^2 = 0.0024$; $P = .03$	EO: $r^2 = 0.012$; $P = .39$
	SAO: $r^2 = 0.024$; $P = .22$	SAO: r^2= = 0.025; $P = .22$

EO, European origin; hs-CRP, high-sensitivity C-reactive protein; LOCF, last observation carried forward; SAO, South Asian origin.

Table IV Safety

Safety Parameters, No. (%)	Unmatched European Origin (n = 1978)	Matched European Origin (n = 63)	South Asian Origin (n = 63)
All-causality AEs	744 (37.6)	16 (25.0)	16 (25.0)
Serious AEs	48 (2.4)	1 (1.6)	0
Discontinuation of study drug because of AEs	84 (4.2)	0	0
Dose reduction or temporary discontinuation because of Aes	61 (3.1)	0	1 (1.6)
Treatment-related AEs	233 (11.8)	1 (2.0)	3 (5.0)
Serious AEs	0	0	0
Discontinuation of study drug because of AEs	65 (3.3)	0	0
Dose reduction or temporary discontinuation because of Aes	19 (1.0)	0	0

AE, adverse event.

in risk factor profile between patients of South Asian and European origin has been noted in prior studies.[1,4] Given the same lipid profile, South Asians had a lower BMI, which was expected based on previously published studies.[17] This finding is consistent with the observation that South Asians have a greater body fat content and more abdominal fat for a given BMI. After controlling for baseline differences, atorvastatin lowered LDL-C and hs-CRP to a similar degree in both groups.

LDL-C lowering with statin drugs has been shown to reduce the incidence of cardiovascular events in both primary and secondary prevention of CHD.[11-13,19,20] However, few patients of South Asian origin have been enrolled in landmark clinical trials, making it difficult to determine if their response to statin therapy in terms of LDL-C lowering and cardiovascular events are equivalent to those reported in populations of European origin.

Asians have historically been considered to be more responsive to the lipid-lowering effects of statins when compared with European populations.[21-23] Ethnic differences in response to statin therapy may be related to differences in pharmacokinetic and pharmacodynamic effects or to potential polymorphisms of genes involved in drug actions or the disease pathways.[24] Although the data on increased response to statin therapy stem primarily from studies conducted in people of East Asian origin, particularly Japanese patients, this has led to the recommendation for lower statin initiation doses in all Asian patients.[25] However, whether these recommendations should also apply to South Asians, a population at high risk for CHD, remains unclear.

An analysis of data from the PRACTICE (Prospective Assessment of Cardiovascular risk and Treatment In Canadians of varying Ethnicity) registry, including 223 patients with CHD, found that atorvastatin and simvastatin, at commonly prescribed doses, modulate LDL-C and HDL-C levels to a similar degree in patients of South Asian (n = 96) or European origin (n = 137).[26] Atorvastatin (median 20 mg/d) produced similar decreases in LDL-C in patients of South Asian (43%) or European origin (41%), as did simvastatin (median 20 mg/d), 35% and 37%, respectively. These results are similar to those found in ACTFAST, where reductions in LDL-C across all atorvastatin dosage groups

combined were not significantly different in patients of South Asian or European origin (38% and 34%, respectively, in the matched case control analysis). These findings suggest that statin dose adjustment may not be warranted in patients of South Asian origin.

Pharmacokinetic studies have shown a 2-fold elevation in rosuvastatin plasma concentration in patients of Asian compared to European origin, and the US Food and Drug Administration (FDA) has recommended the initiation of rosuvastatin at 5 mg/d in Asian patients.[7,8] In the IRIS study (Investigation of Rosuvastatin In South Asian Subjects), exclusively conducted in South Asian patients in North America, usual rosuvastatin and atorvastatin dose ranges (10-20 mg) allowed most patients to reach recommended LDL-C goals.[27] However, this trial did not compare response to therapy in South Asian patients versus that of other ethnic groups. Because of differences in group size and characteristics between the 2 groups in ACTFAST, we only performed high-level comparisons of the safety of atorvastatin. No safety signal was apparent in patients of South Asian origin as compared those of European origin. Thus, atorvastatin appears to be at least as safe in South Asians as it is in patients of European origin.

Hs-CRP has been proposed as an independent cardiovascular risk factor that adds prognostic information to that of conventional risk factors/Framingham risk score.[28] A recent study reported that reducing hs-CRP with a statin in asymptomatic patients with LDL-C below the recommended threshold for therapy led to reduction of cardiovascular events[29]; however, one cannot conclude that the benefit was a result of hs-CRP reduction. Also, there were very few South Asians in this study. We observed no difference in hs-CRP reduction in response to atorvastatin between South Asians and those of European origin. Consequently, should hs-CRP reduction become a target for statin therapy in the future, clinicians do not need to reduce the dose of atorvastatin in South Asians.

Although this ACTFAST ethnicity substudy was prespecified, certain limitations must be considered: the study design was open-label and nonrandomized, leading to dose groups of unequal size; this small subgroup of South Asians may not be representative of the overall South Asian population; the propensity score matching may not account for all potential differences (ie, those unmeasured) between patients of South Asian or European origin; and only one hs-CRP measurement was performed at each time point when the mean of 2 samples taken 2 weeks apart would have been optimal to account for variability in the measurement.[30]

CONCLUSION

These results suggest that the efficacy of atorvastatin in decreasing LDL-C and hs-CRP in patients of South Asian origin is similar to that seen in patients of European origin. The results of this and other studies indicate that lower initiation doses of atorvastatin may not be required in patients of South Asian origin. Considering the high CHD risk in South Asian patients, identification and aggressive management of traditional and emerging CHD risk factors, particularly elevated LDL-C, are a priority.

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